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Case Report

Severe Exacerbation of Liver Disease During Pregnancy in a Thalassemic GBV-C/HGV–Positive Patient and Neonatal Hepatitis in Offspring

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The case of a young woman with GB virus C/hepatitis G virus (GBV-C/HGV) infection and with a severe exacerbation of chronic hepatitis of unknown etiology during pregnancy is described. In the offspring, severe neonatal hepatitis with subsequent mild chronic liver disease of at least 16-month duration was followed by the development of antibodies to the envelope protein (E2) of GBV-C/HGV, suggesting that the child was recovering from GBV-C/HGV infection. There was an improvement in clinical and biochemical parameters in the mother following delivery and alpha-interferon therapy was associated with a transient biochemical response. ***J. Med. Virol. 57:122–125, 1999.***

KEY WORDS: hepatitis G; pregnancy; chronic hepatitis; neonatal hepatitis

INTRODUCTION

A proportion of cases of posttransfusion hepatitis not related to hepatitis A, B, or C have been recently linked to the transmission of GB virus C/hepatitis G virus (GBV-C/HGV). This is a positive-stranded RNA virus that belongs to the *flaviviridae* family. The virus is readily transmitted by transfusion of blood, by some blood products, and by parenteral exposure to blood during intravenous drug use and hemodialysis. Preliminary data obtained by recent studies show a temporal relationship between GBV-C/HGV RNA positivity and transfusion, absence of GBV-C/HGV in non-transfused controls and by donor-recipient linkages [Simons et al., 1995; Leary et al., 1996; Linnen et al., 1996; Wang et al., 1996; Alter et al., 1997; Karayiannis et al., 1997]. GBV-C/HGV infection is generally benign, being responsible for a small number of mild acute and/or chronic hepatitis cases. In the latter case, the natural history and chronic sequelae of infection remain unknown [Alter et al., 1997; Karayiannis et al., 1997]. However, some investigators have claimed possible association of GBV-C/HGV infection with fulminant hepatitis [Yoshiba et al., 1995; Heringlake et al., 1997]. In addition, mother-to-infant transmission of GBV-C/HGV appears to be a common event, unlike the case with hepatitis C virus (HCV) [Feucht et al., 1996; Fischler et al., 1997; Viazov et al., 1997].

We report the first case of a young female thalassemic GBV-C/HGV–positive patient with chronic hepatitis of unknown origin in whom the disease course was exacerbated severely during pregnancy. The infant developed neonatal hepatitis with a protracted course and eventual recovery. The latter was associated with the development of antibodies against the envelope glycoprotein E2 of GBV-C/HGV.

CASE REPORT

The Mother

A 39-year-old woman was referred to the University Hospital in January 1988 because of decompensated liver disease developing in the second month of her third pregnancy. Clinical history was unremarkable

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until 1982, when she became pregnant for the first time. She was found to be anemic at that time and the diagnosis of β-thalassemia minor was made. Spontaneous abortion occurred at 24 weeks of pregnancy, as a result of abruptio placentae. Subsequent vaginal hemorrhage necessitated the transfusion of four units of packed red cells without apparent side effects. At that time, her liver function tests were normal. In 1984, the patient required transfusion of three units of packed red cells during her second pregnancy, and shortly after again because of relapsing anemia. She then delivered at term a normal boy and her liver function tests were still in the normal range. Her third pregnancy began in September 1987; blood examinations showed abnormal liver function tests and she became mildly jaundiced by October. She had not been on medication during the previous months and there was no history of alcohol abuse. Available hematological and biochemical results showed hemoglobin at 10.7 g/dl, aspartate aminotransferase (AST) 736 I.U./l (N < 23), alanine aminotransferase (ALT) 541 I.U./l (N < 32), alkaline phosphatase 97 I.U./l (N < 60), and total serum bilirubin 1.5 mg/dl (N ⩽ 1). In December, increasing asthenia, deepening jaundice, and lower limb edema were observed.

On admission to hospital in January 1988, physical examination revealed an icteric and chronically ill-looking patient. The liver was felt 7 cm below the right and the spleen was 9 cm below the left costal margin. Lower limb edema was present. Obstetric examination was normal. Laboratory tests gave the following values: hemoglobin at 7.8 g/dl, AST 1,480 I.U./l (N < 25), ALT 647 I.U./l (N < 32), alkaline phosphatase 175 I.U./l (N < 60), total serum bilirubin 6.25 mg/dl (N < 1), total serum protein 6.8 g/dl, albumin 3 g/dl, and globulin 2 g/dl. Prothrombin time was 68% (N 70–110). Serum iron level, transferrin saturation, and ferritin level were in the normal range (90 mg/dl, 282 mg/dl, and 252 mg/dl, N 80–160, 260–380, and 100–300, respectively). Plasma ceruloplasmin was increased at 226% (N ± S.D. = 100% ± 30%), as well as serum copper (241 μg/dl; N 80–150), while urinary copper excretion was only slightly higher than the normal range: 95 μg/24 hr (N 15–50). Alpha-1 antitrypsin level was in the normal range. Using commercial immunoassays, serology for hepatitis A (RIA HAVAB M, Abbott Laboratories, North Chicago, IL), hepatitis B (AUSRIA, AUSAB, ABBOT-HBe, and CORAB; Abbott Laboratories), and toxoplasmosis was negative, whereas evidence for past infection with cytomegalovirus (CMV), herpes (Elisa, Behring-Hoechst, Germany) and Epstein-Barr virus (EBV) (IF) was found. Tests for antismooth muscle and antimitochondrial antibodies were negative. Antinuclear antibodies were slightly positive at a titer of 1/160. Hemoglobin electrophoresis showed a typical pattern of β-thalassemia minor: HbA2 4.5% (N < 3), HbF 2.1% (N < 2). Coombs' test was negative.

A percutaneous liver biopsy was carried out a week after admission and showed disrupted lobular architecture with areas of multilobular necrosis, bridging fibrosis and early liver nodular transformation. Hepatocytes isolated by dissecting inflammatory fibrosis exhibited a pseudoglandular rosette pattern. Numerous multinucleated cells were present (Fig. 1).

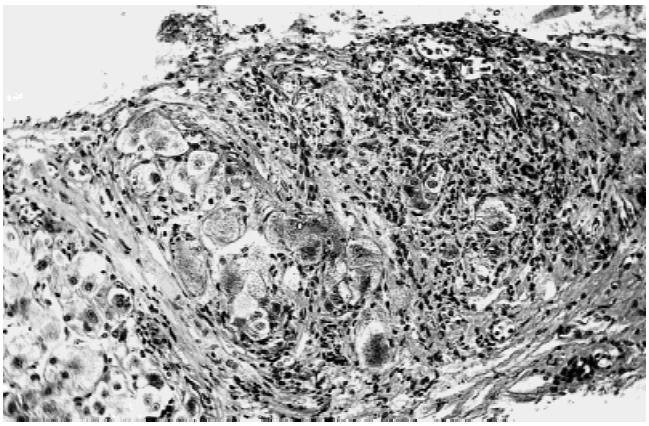

Fig. 1. Liver biopsy of the mother performed at 19 weeks of pregnancy showing disrupted liver architecture, presence of multilobular necrosis, broad infiltrated fibrous septa, and early nodular transformation. The hepatocytes are isolated by dissecting inflammatory fibrosis from pseudoglandular rosettes. Liver cells are swollen and contain bile pigments.

Delivery was induced by ocytocin in May, at 35 weeks of pregnancy. Three units of fresh frozen plasma and 3 units of packed red cells were administered before delivery, which was otherwise uncomplicated, as was the postpartum period.

Treatment with alpha-2b interferon (2.5 million units three times a week, Intron A, Schering Essex) was started 1 week after delivery. Serum transaminase and bilirubin levels rapidly improved after a short and transient rise (Fig. 2). Prothrombin time became normal. The clinical condition of the patient improved rapidly and she was able to resume normal activity.

A year later (May 1989), therapy withdrawal resulted in a slight worsening of biochemical parameters, which remained stable until October 1997 (Fig. 2). HCV antibodies tests (Ortho HCV Elisa) carried out on successive serum samples, including that of October 1997, were negative. HBV DNA and HCV RNA by PCR on sera obtained during pregnancy and during the following years (kept at –80°C) were also negative. Hepatitis E virus serology on sera obtained during pregnancy was negative. In contrast, GBV-C/HGV RNA by PCR [Linnen et al., 1996] was positive on sera obtained in June 1988, January 1990, and September 1995.

The Offspring

Physical examination at birth showed jaundice and hepatosplenomegaly. Laboratory tests gave the following results: total serum bilirubin was 14.5 mg/dl (direct bilirubin: 7.17 mg/dl), and liver enzymes were elevated (AST: 726 I.U./l; ALT: 130 I.U./l; γGT: 53 I.U./l; alkaline phosphatase: 409 I.U./l). Total serum protein was 6.3 g/dl (albumin: 3.6 g/dl, globulin: 1.3 g/dl). Prothrombin time was normal. Extensive viral cultures of saliva,

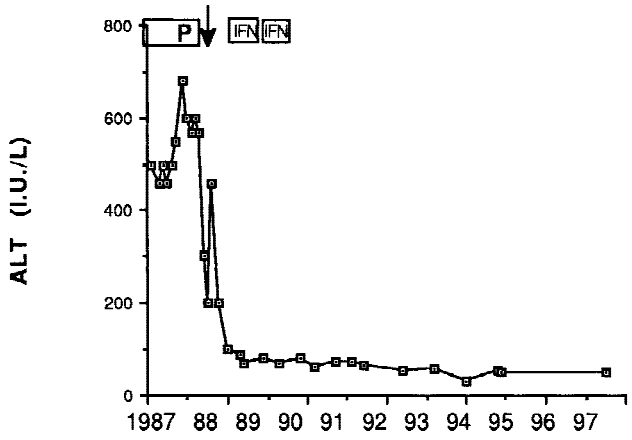

Fig. 2. ALT profile of the mother over time. P: pregnancy; ↓ delivery; and IFN: interferon therapy.

urine, and stools were negative. Serology for hepatitis A, B, and CMV was negative, but antibodies for rubella, herpes, and EBV were detectable. These were of IgG clases and therefore passively acquired from the mother. Metabolic type hepatitis was excluded on the basis of blood and urine chromatography for amino acids and organic acids, urydil galactose transferase determination, alpha-1 antitrypsin level, and phenotype and blood chromatography for bile acids.

The clinical course during the first two weeks of life was marked by a poor weight gain, severe cholestasis, jaundice, and persistent hepatosplenomegaly (Fig. 3).

A needle liver biopsy was undertaken at two weeks of age. The lesions were considered typical of severe neonatal hepatitis. Portal tracts were enlarged by fibrosis, mildly infiltrated by lymphocytes and some neutrophils, and showed moderate bile duct proliferation. The limiting plate was disrupted. In the lobules, there was prominent hepatocellular swelling and multinucleation together with a few necrotic cells, mild lymphocytic and neutrophilic infiltration. There was also severe cholestasis (Fig. 4).

From this point, the clinical and biological course progressively improved. At 8 months of age, a second needle liver biopsy was carried. Liver histology had improved strikingly, and the overall architecture was normal. There was occasional disruption of the limiting plate of portal tracts. In the lobules, some small areas of collapse, a few acidophilic bodies, and rare swollen hepatocytes were observed (Fig. 5). Liver function tests returned to normal within a short period of time (Fig. 3).

Tests for HBV DNA and HCV RNA were persistently negative. Polymerase chain reaction for GBV-C/HGV RNA performed on serum obtained in January 1991, which was kept at –80°C, and in September 1995 was also negative. However, these two sera were tested using the anti-HGenv test recently developed by Boehringer Mannheim in Germany [Tacke et al., 1997] and both were found to be positive. Unfortunately, there was no serum available before 1991 for GBV-C/HGV RNA testing.

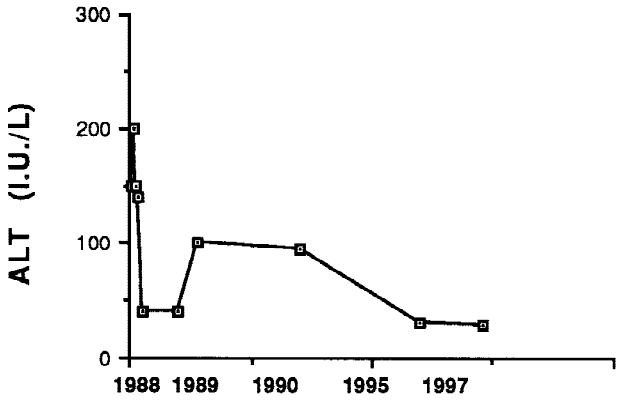

Fig. 3. ALT profile of the infant.

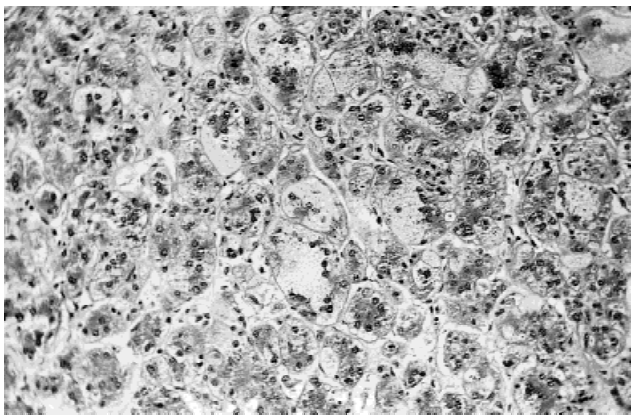

Fig. 4. Liver biopsy of the infant performed at two weeks of age showing prominent hepatocellular swelling and multinucleation together with mild inflammatory infiltrate.

DISCUSSION

A young GBV-C/HGV–positive woman is described who developed a severe exacerbation of her chronic liver disease of unknown origin during her third pregnancy. Her infant developed severe neonatal hepatitis, which ran a protracted course, with eventual recovery and development of antibodies to the envelope glycoprotein E2 of GBV-C/HGV. These antibodies are present in individuals who have recovered from infection and are absent in viremic patients [Pilot-Matias et al., 1996; Tacke et al., 1997]. The detection of anti-E2 suggests that the child had recovered from GBV-C/HGV infection. The evidence therefore suggests infection with GBV-C/HGV of the infant from the mother, which in the former led to recovery. Vertical transmission has been shown to occur in over 50% of cases studied so far [Feucht et al., 1996; Fischler et al., 1997; Viazov et al., 1997], an incidence of infection which is much higher that that for HCV.

Although hepatitis exacerbation in the mother and the neonatal hepatitis in the child were likely related to GBV-C/HGV infection, we cannot exclude the possibility that the GBV-C/HGV infection was coincidental and that a second agent present in the mother and

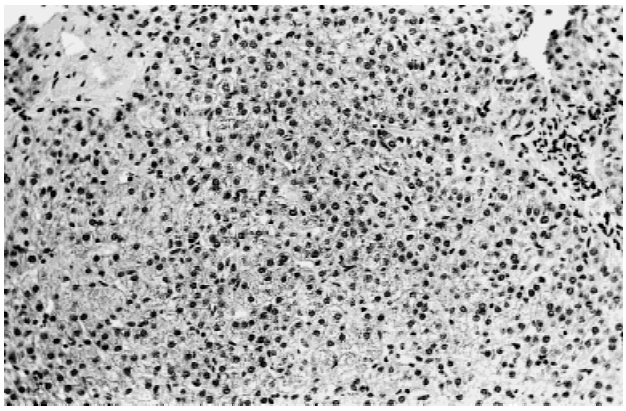

Fig. 5. Liver biopsy of the child performed at 8 months of age showing normal architecture and mild lobular changes.

transmitted to the child may have been responsible for the hepatitis. Such a circumstance has been suggested as an explanation for the low frequency of hepatitis related to GBV-C/HGV infection; only 25% of cases of acute posttransfusion GBV-C/HGV infection [Wang et al., 1996; Alter et al., 1997] and 40% of cases of persistent GBV-C/HGV infection [Karayiannis et al., 1997].

In conclusion, this case report suggests the existence of a non-B, non-C blood-borne transmissible agent, which may be responsible for chronic hepatitis exacerbating during pregnancy and capable of transplacental transmission. Even if this event cannot be related with certainty to GBV-C/HGV, such a possibility should be considered in the counseling of GBV-C/HGV–positive women of childbearing age.

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